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14. ABSTRACT

The purpose of this postdoctoral training award is for the PI to be trained in every aspect of conducting a research breast cancer study in a clinical setting. This study aims to improve specificity of breast cancer detection by using a combined MRI/MRS protocol. In the past year, the final year of this award, the PI has performed the following tasks independently: renewing IRB, recruiting and consenting patients, MRI/MRS data acquisition, and data analysis. A total of 20 patients were recruited for the study in the past year. The results from these 20 subjects and previously recruited subjects (50 from the preliminary data in the grant application and 43 recruited with the support of this grant) show 100% sensitivity and 100% specificity of the combined MRI/MRS protocol.

15. SUBJECT TERMS
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Introduction

This is the final report for a Breast Cancer Research Program (BCRP) post-doctoral training grant, covering the period from July 2007 to July 2008.

The approved Statement of Work of this award is listed as the following:

Task 1. *Training in patient recruitment and MRI/MRS scanning protocol, Months 1-6:*

- *a.* *Interacting with radiologists and surgeons at breast care center.*
- *b.* *Preparing advertising flyers and learning patient recruitment procedure.*
- *c.* *Learning consenting patients.*
- *d.* *Training in MR scanning of patients, including DCE MRI, ^{1}H MRS and perfusion MRI. Number of patients = 25.*
- *e.* *Training in MR data processing and correlation of MR data with biopsy results*

Task 2. *Extensive evaluation of the sensitivity and specificity of the proposed MRI/MRS protocol in detection of breast malignancy, Months 7-36:*

- *a.* *Scanning 125 patients with the MRI/MRS protocol.*
- *b.* *Creating and maintaining data base for MR data and biopsy results.*
- *c.* *Coordinating between research subjects and their physicians in regards of clinical and research matters related to the study.*
- *d.* *Analyzing MR data, correlating MR results with biopsy results, computing overall sensitivity and specificity of the MR protocol in detection of breast malignancy.*
- *e.* *Preparing for publication of research results.*
- *f.* *Fine-tuning and optimizing the procedure of MR data acquisition and processing, establishing a clinically practical MR protocol with improved specificity for diagnosis of breast cancer.*

During the first year of the award from May 2004 to May 2005, we accomplished Task 1 and more as described in the previous annual report, except that we were unable to recruit patients due to extra time needed to gain IRB approval. The IRB protocol for this study was finally approved by the Army Surgeon General's Human Subjects Research Review Board and the local Stony Brook University IRB Committee in December 2005. From January to May 2006, 8 subjects were recruited for this study, which was reported in the 2006 annual report. From June 2006 to July 2007, a total of 35 subjects were recruited. The results show promising 100% sensitivity and 100% specificity of this combined MRI/MRS method in breast cancer diagnosis. This was reported in the 2007 annual report. At that time, a no-cost extension of this grant was requested and approved for another year to allow us to recruit more patients as proposed in the original application.

Body

With the help of the mentor, Dr. Wei Huang, the collaborator, Dr. Paul Fisher, and the DOD representatives, the PI has made the following progress in the past year:

1. Through interactions with the DOD representative on IRB protocol issues and local IRB committee, the PI repeatedly made modifications to the IRB protocol, consent form, and the advertising pamphlet.
2. The PI successfully renewed the IRB protocol for this study in June 2007.
3. The PI independently performed the following tasks for the 20 subjects recruited for this study: patient recruitment and consent, MRI/MRS data collection and analysis, correlating MR results with pathology results.
4. The results of the proposed MRI/MRS protocol from a total of 113 patients so far show promising 100% sensitivity and 100% specificity in detection of breast malignancy.
5. The PI has created and is maintaining a secure data base that includes the MRI/MRS results and the corresponding pathological findings. Each subject is labeled with a three-digit number, such as 001, 002 … 010, etc.
6. Mostly because of the PI's involvement in breast cancer MRI research, the PI was offered and has accepted a position of Assistant Professor in the Radiology Department, Oregon Health & Science University (OHSU). The PI would like to express her gratitude for this postdoctoral grant support in furthering her career in breast cancer research.
7. The PI has left State University of New York at Stony Brook in July 2008 and will join OHSU in September 2008. The IRB for this project has been terminated.

Key Research Accomplishments

- Independently perform the tasks of MR data collection, data analysis, patient recruitment and consent for a clinical research study.
- Independently renewed IRB protocol, consent form and advertising pamphlet.
- Successfully recruited and obtained data from 20 subjects in the past year, and a total of 63 subjects during the grant period.
- Oral and poster presentations in the 2005 and 2008 Era of Hope meetings.
- Poster presentation at the 2006 meeting of International Society for Magnetic Resonance in Medicine.
- Manuscript in preparation for submission to the journal of Radiology.

Reportable Outcomes

20 patients with positive mammography findings were recruited to participate in this study last year (113 patients total for this study, including the 50 patients studied as preliminary data for the application of this grant). Biopsy of the suspicious lesion was performed after but usually within a week of the MR examination.

The MRI/MRS protocol was conducted with a 1.5 T Philips Intera whole-body scanner with the body coil as the transmitter and a dedicated phased array breast coil as the receiver. For dynamic contrast enhanced (DCE) T_1-weighted MRI, a 3D SPGR sequence was employed to acquire 8 frames of sagittal volumetric images of the whole breast with the suspicious lesion(s), with 30^o flip angle, TE = 3.8 ms, TR = 9 ms, 3-5 mm slice thickness, 24 cm FOV and 64x256 matrix size. Usually each frame included 18-26 slices and the acquisition time for each frame was less than 16 sec. Gd contrast agent (0.1 mmol/kg dose) was delivered at 2 cc/sec by IV injection at the start of the second frame acquisition. The images of the first frame were subtracted from images of every frame. Rapid contrast enhancement in lesions with signal intensity reaching plateau by the fourth frame was defined as positive finding. Any enhancement with continuous rising of signal intensity through eight frames or no enhancement was defined as negative finding. Examples of DCE MRI signal intensity time course are demonstrated in Figure 1. The study was discontinued for patients with negative findings. Patients with positive findings, with further consent, continued to undergo ^{1}H MRS and perfusion MRI examinations.

Single-voxel proton spectrum was collected from the enhanced lesion with a PRESS sequence, TE = 135 ms, TR = 2 s, and 128 scan averages. Perfusion MRI was performed on a 5-mm single sagittal slice containing the enhanced lesion with a T_2*-weighted FLASH sequence, 10^o flip angle, TE = 35 ms, TR = 54 ms, 24 cm FOV, 92x256 matrix size, and 40 frames. IV injection of Gd contrast agent (0.1 mmol/kg) was carried out at 4 cc/sec during perfusion MRI acquisition. The detection of an apparent choline compounds (Cho) peak (S/N > 2) at 3.23 ppm was defined as positive finding for the MRS study, negative otherwise, as shown in Figure 2. The relative blood volume map was generated from the perfusion imaging data. The striking enhancement in the lesion area on the map compared to normal tissue area was defined as positive finding for the perfusion MRI study, negative otherwise (Figure 3).

The MR and pathology results for the total of 113 patients are summarized in the Table.

Table MRI/MRS and Pathology Findings of Suspicious Breast Lesions

Patient No.	DCE MRI	MRS	Per. MRI	Path.
13	+	*	*	Malignant
39	-	*	*	Benign
37	+	+	+	Malignant
13	+	-	-	Benign
5	+	+	-	Benign
4	+	-	+	Benign
2	+	+	*	Benign

Per. = perfusion; Path. = pathology; + = positive findings; - = negative findings; * = MR scans discontinued due to negative DCE MRI findings or at patient's request.

DCE MRI alone demonstrates 100% sensitivity and 62% specificity. With the addition of the MRS, the specificity improves to 89%. With further addition of perfusion MRI and the assumption that any negative finding from the two methods (MRS and perfusion MRI) renders final finding negative for the combined MRI/MRS protocol, the specificity improves to 100% (excluding two patients with MRS but without perfusion MRI data). This clinically practical MRI/MRS protocol has the potential to reduce possibly unnecessary (benign) biopsies in the future.

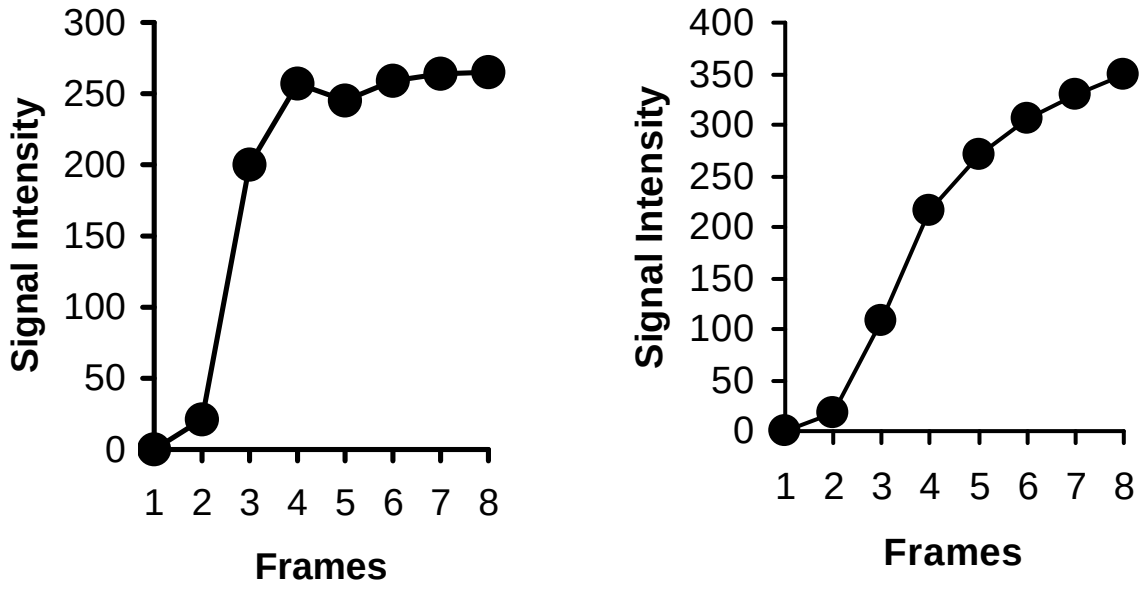

Figure 1. Examples of DCE MRI signal intensity time course: (Left) Plot of image signal intensity versus image frame number obtained from the enhanced lesion area. The curve rose rapidly following contrast injection, reaching plateau by the fourth frame --- positive finding. (Right) The same type of plot as in the left panel. The curve rose continuously through the time course of DCE MRI data acquisition --- negative finding.

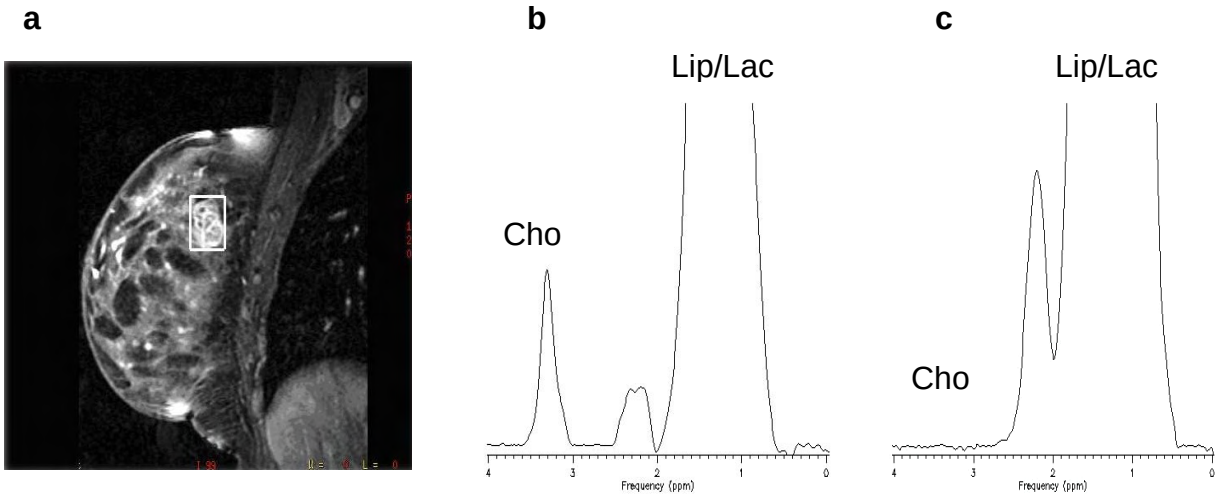

Figure 2. (a) The rectangular box encompassing the enhanced lesion demonstrates the placement of MRS voxel for the single-voxel ^{1}H MRS study. (b) Magnified proton spectrum acquired from the region of a pathologically proven malignant breast tumor. The spectrum was collected with a PRESS sequence (2000/135). An apparent Cho (choline-containing compounds) peak was detected at 3.23 ppm. (c) The same type of magnified proton spectrum as in panel b, collected from the region of a pathologically proven benign lesion. No Cho peak was detected with only noise-level signal at 3.23 ppm. Lip: lipid, Lac: lactate.

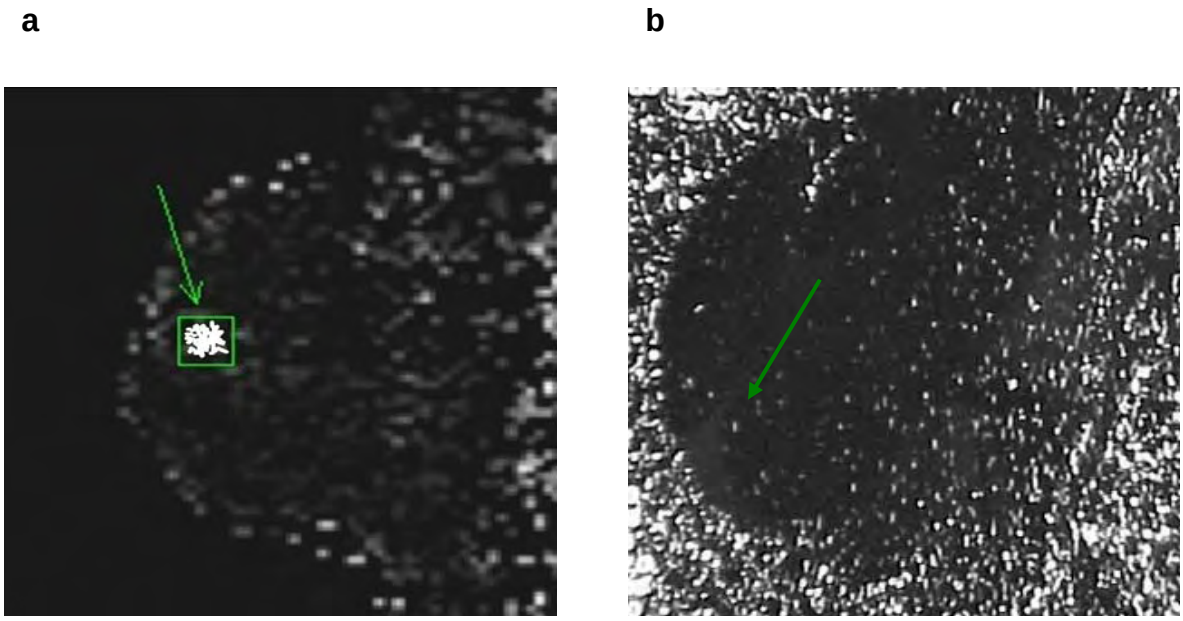

Figure 3. The relative breast blood volume maps reconstructed from the T_2*-weighted perfusion MRI studies: (a) Compared to normal breast tissue areas, hyperintensity was observed in the region of a pathologically proven malignant tumor (arrow). (b) No enhancement was seen in a pathologically proven benign lesion (arrow), even though contrast enhancement was observed in the same lesion in the T_1-weighted DCE MRI study.

Conclusions

From July 2007 to July 2008, the PI independently perform the tasks of IRB renewal, patient recruitment and consent (n = 20), MRI/MRS data acquisition, and data analysis. The results from a total of 113 patients show promising 100% sensitivity and 100% specificity of the proposed MRI/MRS method in breast cancer detection. This clinically practical MRI/MRS protocol has the potential to reduce possibly unnecessary (benign) biopsies while not missing any cancer detection in the future. The updated results were presented at the 2008 Era of Hope meeting in June 2008, Baltimore, Maryland.

This postdoctoral grant support has significantly helped the PI in furthering her career in breast cancer research. The PI has accepted an Assistant Professor position in the Radiology Department, Oregon Health & Science University (OHSU). She will continue to pursue her goals in the field of breast cancer research.

Appendices

2008 Era of Hope Abstract

CLINICALLY PRACTICAL MAGNETIC RESONANCE IMAGING/SPECTROSCOPY PROTOCOL FOR IMPROVED SPECIFICITY IN BREAST CANCER DIAGNOSIS

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Conventional mammography is known to have high false positive rate (60-80%) in detection of breast malignancy, resulting in unnecessary biopsies. The increasingly popular dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) technique demonstrated high sensitivity (88-100%), but rather variable specificity (37-97%) in diagnosis of breast cancer. In this study, a combined MRI/MR spectroscopy (MRS) protocol including DCE MRI, 1H MRS, and perfusion MRI was used to examine patients with suspicious breast lesions. By correlating MR data with pathology results, we sought to determine if this clinically practical MRI/MRS protocol improves the specificity in detection of breast malignancy.

113 patients with positive mammography findings were recruited to participate in this MR study thus far. Biopsy was performed after but usually within a week of the MR examination. The MRI/MRS protocol was conducted with a 1.5 T MR scanner. For DCE MRI, 8 series of sagittal volumetric images of the whole breast with suspicious lesions were acquired with a temporal resolution of about 15 sec. Gadolinium-based contrast agent (0.1 mmol/kg dose) was delivered by intravenous (IV) injection at the start of the second series acquisition. Rapid contrast enhancement in lesions with signal intensity reaching plateau by the fourth series was defined as positive finding. Any enhancement with continuous rising of signal intensity through eight series or no enhancement was defined as negative finding. The study was discontinued for patients with negative findings. Patients with positive findings continued to undergo single voxel 1H MRS and perfusion MRI examinations. The detection of an apparent choline (Cho) peak (signal-to-noise ratio > 2) at 3.23 ppm was defined as positive finding for the MRS study. Another IV injection of contrast agent (0.1 mmol/kg) was administered during perfusion MRI acquisition. The relative blood volume map was generated from the perfusion imaging data. The striking enhancement in the lesion area on the map compared to normal tissue area was defined as positive finding for the perfusion MRI study.

By correlation with the pathology results as the reference standards, there were no false negative findings from DCE MRI studies, showing 100% sensitivity of this method. The specificity of DCE MRI was 61%. With the addition of 1H MRS data, the specificity improved to 90%. With further addition of perfusion MRI results, the specificity improved to 100%. This study shows that while DCE MRI has very high sensitivity in diagnosis of breast cancer, its specificity is unsatisfactory. The MRI/MRS protocol of combined use of DCE MRI, 1H MRS and perfusion MRI substantially improves specificity and may help to reduce unnecessary biopsies following positive mammograms. With its technology easy for implementation at any imaging site and short scanning duration, this MRI/MRS protocol may have the potential to become the standard screening tool following positive mammographic findings.